THE MAGAZINE OF THE WORLD HEALTH ORGANIZATION

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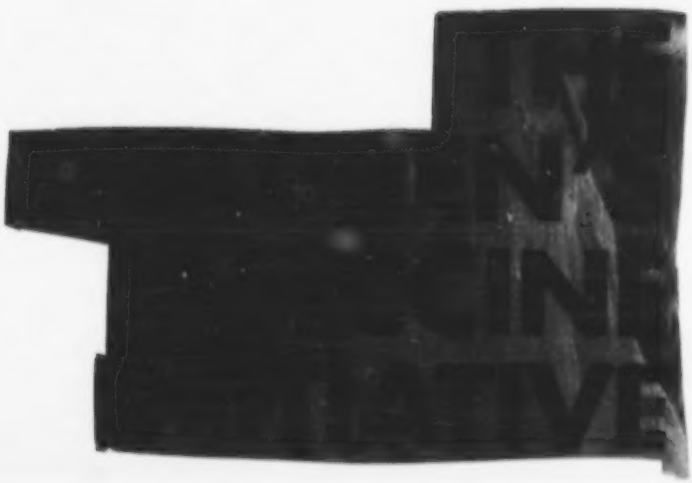

WORLD HEALTH
THE MAGAZINE OF THE WORLD HEALTH ORGANIZATION

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Editorial

Hope for the future

Mr James P. Grant, Executive Director of UNICEF.

Ten years ago nearly five million children died each year from diseases preventable by the vaccines used in the Expanded Programme on Immunization. During the past decade this toll on young lives has been reduced dramatically through increasing the coverage of immunization for measles, DPT (diphtheria, pertussis and tetanus), poliomyelitis, and tuberculosis (BCG) in children during their first year of life. Deaths from neonatal tetanus are also being reduced by immunizing women during or prior to pregnancy. Immunization coverage in developing countries increased nearly fourfold from a base of approximately 20% in 1981 to reach the 1990 goal of 80% globally. WHO estimates that 3.2 million young lives were saved from measles, neonatal tetanus and pertussis in 1990 alone. Immunization programmes now reach more than 100 million infants each year.

However, approximately 2.1 million children are still dying annually from the diseases that are preventable with the six existing Expanded Programme on Immunization vaccines. True, universal protection has not yet been achieved, since the vaccines are not 100% effective or are given too late, infants or their mothers do not receive the full series and become "dropouts", or some vaccines lacking adequate stability to withstand heat become impotent before use.

Each year an additional estimated 7 million deaths from bacterial and viral diseases, such as bacterial diarrhoea, meningococcal meningitis, hepatitis A, C and E, and rotavirus, dengue and acute respiratory infections, could be prevented with new vaccines. Many of these vaccines have already been developed or could be developed with existing technology. Several could potentially be incorporated into the Expanded Programme on Immunization by mid-decade. Millions of additional lives would also be saved each year if effective vaccines against malaria and other important diseases were developed.

The international community has forged a new alliance, called the Children's Vaccine Initiative, to guide the use of new technology and facilitate the development of new and improved vaccines to control these diseases. The Initiative was founded by five organizations: the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), the World Bank, the Rockefeller Foundation, and the World Health Organization (WHO). Working together under the Children's Vaccine Initiative "umbrella" are governments, nongovernmental organizations, international and national public health and research agencies, public and private foundations, and research groups and teams from private industry.

Dr Hiroshi Nakajima, Director-General of the World Health Organization.

The Initiative is moving ahead with research and development of a heat-stable oral poliomyelitis vaccine, a single-dose tetanus toxoid vaccine, and an improved measles vaccine which can be given earlier in life. Task forces are analysing the global vaccine supply situation and are working with both public and private sector institutions to ensure that high-quality, low-cost vaccines will be available to meet the goals for the 1990s.

Although the work has just begun, the Children's Vaccine Initiative offers an opportunity for the international community to work together, using our knowledge, resources, energy and, above all, our sense of humanity to fulfil the promise of new vaccines which will save the lives of millions of young children and contribute towards the eradication or elimination of diseases such as poliomyelitis and measles. ■

James P. Grant

Hiroshi Nakajima, M.D., Ph.D.

James P. Grant
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The Children's Vaccine Initiative

Frank Hartvelt

Beyond the immediate objectives of the CVI is the ultimate goal of a single oral immunization shortly after birth that will protect the world's infants against all major childhood diseases.

In September 1990, two historic events took place which represented a quantum leap forward for child survival and development. At the World Summit for Children, presidents, prime ministers and other representatives of 159 countries agreed to step up efforts and set specific targets to improve the condition of the world's children in vital areas affecting their development: health, education, and children's rights. The targets to be reached by the year 2000 were considered to be feasible and financially affordable. The overall goal for health, set globally, was to reduce child mortality among under five-year-olds by one-third, by the year 2000.

A less publicized event occurred a few weeks before the World Summit, when an international group of experts in the field of vaccine research and application reviewed the contribution which improved and new vaccines can make during the current decade to the health of the world's children. The resulting "Declaration of New York" provided the scientific and industrial underpinning for the goal of childhood mortality reduction set by the world leaders. It stated specifically that the application of current science can lead to vaccines which can be given earlier in life, require one or two rather than multiple doses, keep their potency in tropical temperatures, can be given in the form of cocktails of several vaccines, and are affordable.

"Vaccines offer the greatest prospects for achieving rapid improvements in health."

Dr O. Ransome-Kuti, former Minister of Health, Nigeria.

In 1991 the Rockefeller Foundation, the United Nations Development Programme (UNDP), UNICEF, the World Bank and WHO launched the Children's Vaccine Initiative (CVI), joining their forces with vaccine research and development institutes, pharmaceutical companies, and national and international development agencies. The resulting international coalition is unique in the goals set, its broad mandate, and the synergy of the activities of its national and international partners. Set against the ultimate goal of a single oral immunization shortly after birth that will protect the world's infants against all major childhood diseases, the immediate objectives of the CVI are:

- to facilitate provision of an adequate supply of affordable, safe and effective vaccines against important infectious diseases;
- to accelerate the development and production of improved and new vaccines;
- to simplify the complex logistics of vaccine delivery.

Management structure

What has happened since the incep-

The need for better and new vaccines

Despite the dramatic rise in childhood immunization over the past 15 years – up to 80% in many countries – avoidable illness and deaths among children are still high.

Improvement and development of existing and new vaccines against bacterial and viral diseases could save the lives of an estimated 8 million children and prevent 900 million severe illnesses among children annually.

Developing countries are making progress towards producing high quality vaccines.

tion of the CVI? Its partners have moved ahead on three accounts: establishing an organizational structure to guide and manage the CVI activities, initiating a strategic planning process, and developing a heat-stable poliomyelitis vaccine and a single-dose tetanus toxoid vaccine.

Today the CVI organization includes: a Consultative Group which provides an international forum for consultation and review; a Management Advisory Committee to review strategies and programmes (a microcosm of the much larger consultative group); a Standing Committee composed of the five founding agencies, which takes its cue from the other bodies in approving the CVI strategy, work programme and budget; and, at the operational level, Product Development Groups designed to promote, facilitate and manage projects leading to the development of vaccines and related products. A secretariat, based in WHO, Geneva, supports the CVI bodies as outlined.

Over the past year, two Product Development Groups have already made substantial progress in developing a heat-stable poliovaccine (linked to the poliomyelitis eradication goal) and a single-dose tetanus toxoid vaccine, the latter with the potential to prevent 600 000 deaths per year.

According to WHO senior officials and scientists familiar with international health programmes, the take-off phase of the CVI has been remarkably smooth. In fact, hundreds of highly motivated specialists are already working worldwide to push frontiers ahead in strategic planning, biotechnology, immunology, epidemiology, vaccine supply, quality control, regulatory matters, licensing, patents, and financial and legal issues. All these areas are interlocking parts of a complex mosaic.

The CVI relies heavily on "upstream" vaccine research carried out by the WHO/UNDP Programme for Vaccine Development, and on the "downstream" operations and experience of the global Expanded Programme on Immunization (EPI) spearheaded by UNICEF and WHO which, by the end of 1990, reached 80% of the world's children with a protective course against the six major childhood diseases: poliomyelitis, measles, tuberculosis, diphtheria, pertussis, and tetanus. To make the EPI more effective the CVI aims to improve the heat stability of vaccines (e.g., poliomyelitis) and to reduce the

"A new relationship is needed between the public sector and industry to combat poverty."

Mr J. P. Pronk, Minister of Development Cooperation, the Netherlands.

CVI: For the sake of children

The Children's Vaccination Initiative (CVI) is an informal association of public and private groups dedicated to helping the world community to focus, accelerate and apply advances in the science, development, manufacture and efficient delivery of new and better vaccines for the world's children.

It was launched in response to the Declaration of New York, made shortly before the World Summit for Children in 1990, which called for a global commitment to the production and delivery of "ideal children's vaccines" that provide lasting protection against a wide range of diseases, are simple to administer and are affordable.

The CVI was established by the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), the Rockefeller Foundation, the World Bank and the World Health Organization (WHO), and has its secretariat at WHO's headquarters.

A news bulletin called *CVI Forum* is published three times a year and is available on request from Dr Lindsay Martinez, CVI Secretariat, WHO, 1211 Geneva 27, Switzerland.

Contributors to the CVI

To date, the following agencies and countries have made specific financial contributions: the founders – the Rockefeller Foundation, the United Nations Development Programme (UNDP), UNICEF, the World Bank, WHO – the Association for Cooperation in International Health (Japan), Canada, the European Community, Japan, the Netherlands, Rotary International and the USA. In addition an increasing number of countries, agencies and companies are undertaking activities under the CVI umbrella.

number of doses through the administration of vaccine cocktails. The implications are not only that more infants are reached but also that the cost of logistics, especially the cold chain, will decline, thereby potentially freeing funds for vaccine development and production and higher immunization levels.

Among the constraints faced by the CVI are the soaring costs of vaccine development and production, due to the high cost of industrial research and development through increasingly sophisticated technologies (e.g., genetic engineering), and the high insurance premiums that companies must pay against lawsuits stemming from possible side-effects. Another factor is the increased concentration of vaccine development and production in a few conglomerates which could lead to cartel price-setting. On the positive side, as suggested by large international vaccine manufacturers, a two-tier price structure is needed with a market price for developed countries and an affordable price for developing countries.

In the scientific arena, exciting developments are anticipated in micro-encapsulation whereby a vaccine contained in microcapsules is injected and – since the capsules are biodegradable – is released over time, mimicking repeated injections. The live-vaccine-carrier approach is a second path towards a one-shot vaccine; unrelated live viral or bacterial components will be used as carriers to deliver the required vaccines more efficiently. A third approach is to use micro-encapsulation and live-vaccine carriers for oral administration, thereby obviating the complex logistics of injections.

Although private sector companies have shown much interest in the CVI, their concrete participation has yet to materialize. The dilemma to be overcome is to match corporate profits with public health goals; so national and international agencies may need to guarantee large vaccine purchases over a period of years in order to induce companies to develop and produce them. More attention needs to be directed to building the capacity of developing countries to produce high quality vaccines and establish quality control mechanisms.

From a wider development perspective, immunization must go hand in hand with not only improvements in health services, water supply and sanitation, nutrition, family planning and education, but also economic development which – in the industrialized countries – virtually eliminated infectious diseases in recent history. Visionary initiatives like the CVI can have an enormous impact on human development within this larger picture. ■

CVI target diseases

EPI vaccines

Tetanus toxoid
Heat-stable poliomyelitis
Measles
Pertussis (whooping cough)
Hepatitis B

Licensed non-EPI vaccines

Haemophilus influenzae type B
Meningococcus
Pneumococcus
Typhoid

Unlicensed vaccines likely to be available within the next five years

Dengue
Enterotoxigenic E. coli
Rotavirus

Under consideration

Malaria
Shigella
Tuberculosis

"Every day thousands of children die because they are not immunized. Conventional approaches must change to respond to the explosive demand for vaccines."

Dr A. Mérieux, President and Director-General, Pasteur Mérieux Serums and Vaccines of France.

In the foreseeable future, children under five will be vaccinated against a whole range of other diseases.

Mr Frank Hartvelt is Deputy Director of the Division for Global and Interregional Programmes, United Nations Development Programme (UNDP), One United Nations Plaza, New York, NY 10017, USA.

Prospects for new vaccines

Sir Gustav Nossal

Vaccine trial in progress in India.

One of the major triumphs in world health has been the establishment of an infrastructure for immunization covering over 80% of all the world's children. Now that vaccines, the most cost-effective invention of scientific medicine, can reach nearly all these children, we must capitalize on this hard-won development both by simplifying vaccination procedures and by widening the range of communicable diseases covered by immunization programmes. Intensive research in many countries holds great promise for rapid progress in both these fields.

The improvement of vaccine efficiency and the simplification of vaccine delivery systems constitute a new specialty in immunology called trans-disease vaccinology. Three areas of this new science are especially important.

The first is the use of highly attenuated harmless viruses or bacteria to carry vaccine molecules or *antigens* derived from a disease-causing organism into the body. This exciting line of research depends on genetic engineering. For example, the cowpox virus (vaccinia) can be manipulated so that a gene or piece of DNA from a malaria parasite is stitched into it. When the engineered vaccinia virus divides, it also makes the malarial protein coded by that bit of malarial DNA. Of course, the malaria gene has to be chosen with great care to ensure that an immune response to that particular protein truly is protective.

Since the vaccinia virus, so successfully used to eradicate smallpox, occasionally causes bad reactions, the search has widened to find even safer vectors. The canary-pox virus seems extremely promising. So do several types of bacteria.

In principle, there is no reason to limit the engineering to just one gene. Indeed, for a wily parasite like malaria it would make sense to combine several key genes and create a cocktail vaccine, so that the parasite would be attacked on several fronts. Moreover, why limit the approach to just one disease? It is possible that a single harmless virus or bacterium could be the vector for genes from several pathogens and thus for a combined vaccine against several diseases.

Provoking immunity

Another trick under active investigation is to include within the transplanted gene package one or more genes designed to strengthen the immune response. During an infection, we elaborate a variety of hormone-like growth-promoting substances called interleukins. These help to make our white cells divide and to do their job better; they promote inflammation and immunity. When interleukin genes are transplanted together with vaccine genes into a live virus vector, this engineered strain can now provoke immunity even in animals with a weakened immune system. Potentially, this would be an important feature for a vaccine used in countries where malnutrition is rife.

Genetic engineering also underlies another major approach to new vaccines. Critical vaccine molecules or antigens, instead of being purified from a cultured organism, can be mass-produced in fermenters using genetically engineered bacteria, yeasts or other harmless cells as tame slaves to manufacture any desired quantity. Such pure proteins have many advantages over crude extracts, but they usually provoke only weak immune responses. Research is under way worldwide on so-called adjuvant substances, chemicals given with antigens to increase vaccine potency. Several adjuvants suitable for human use are at the trial stage.

A second fertile area of research is to improve the way in which vaccines are given. For many current vaccines, three or even four administrations are required. It would be enormously helpful if one "shot" sufficed. An approach to single-dose vaccination is

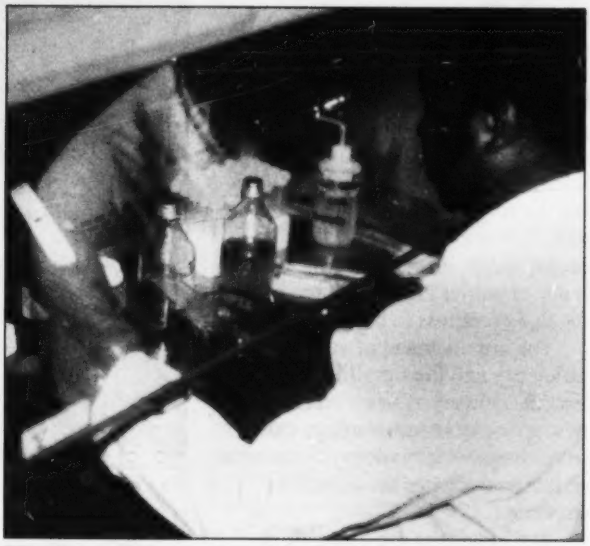
to control the release of antigen molecules following injection. For example, tetanus toxoid could be incorporated into microspheres of varying chemical compositions, some releasing their contents quickly and others only after a delay, thus mimicking a "booster" injection.

A third challenge is to figure out a way to get the immune response maximally active where you want it. Ideally, an influenza vaccine would neutralize the virus in the respiratory tract; a cholera vaccine should direct immunity to the gut; and vaccines against sexually transmitted diseases should protect the urogenital tract.

New and improved vaccines

WHO is now giving great emphasis to sponsoring research on new and improved vaccines for the major viral, bacterial and parasitic diseases. There is much promising news to report. For example, the WHO/UNDP Programme for Vaccine Development (PVD) recently sponsored clinical trials for both group B and group A/C meningococcal vaccines of particular importance in combating meningitis epidemics. If successful, these could be integrated into the Expanded Programme on Immunization. Other major research targets of this exciting international PVD programme include new measles vaccines for early infancy, since current vaccination leaves a gap at the stage where maternally derived antibodies have only just decayed; vaccines for bacterial

Malaria vaccine research at the University of São Paulo, Brazil.



The Institute of Primate Research of Kenya has started trials with a vaccine against leishmaniasis.

Towards a single vaccine for children

Every year, eight million children die in developing countries from viral and bacterial diseases, and 900 million are severely ill.

Viral diseases which kill more than three million children every year include measles (1.5 million deaths); rotaviral enteritis (800 000 deaths); poliomyelitis; hepatitis A and E; dengue (30–60 million infections); Japanese encephalitis (one million infections with 10 000 deaths) and acute respiratory viral diseases.

Bacterial diseases, resulting in the death of over five million children a year, include tetanus (800 000 newborn infants); meningococcal meningitis; bacterial diarrhoeal diseases (more than 1.6 million deaths from shigella, cholera, *Escherichia coli* and typhoid); pneumococcal pneumonia (the leading cause of death from acute respiratory illness); and tuberculosis, which infects both children and adults (over 2.5 million deaths).

These tragedies could be largely prevented by new and improved vaccines, and the international community is joining forces to make this a reality in the 1990s. In 1984 the WHO/UNDP Programme for Vaccine Development (PVD) was created to coordinate international efforts with academic institutions or with other scientific groups. In 1991, the Children's Vaccine Initiative was launched to intensify those efforts. A major objective is to involve the developing countries; 540 scientists from 86 countries have so far been trained, and funds provided for the PVD have supported a total of 87 vaccine development projects in 19 countries.

Research using a wide range of techniques is being carried out with a visionary goal in mind – that of perfecting a "children's vaccine", a one-shot multiple vaccine, preferably given orally, which would protect every child for life against all important infectious diseases. Such an advance would simplify vaccination programmes in developing countries and help to save millions of children from sickness and death.

A protective innoculation is given to a baby in Ethiopia.

diarrhoeal diseases such as cholera, bacillary dysentery and enterotoxic *E. coli*, vaccine for viral diarrhoeal diseases such as rotaviruses; tuberculosis vaccines more efficient than BCG; and vaccines for dengue and Japanese encephalitis. Heartening progress is being made on many of these fronts.

In the parasitic diseases field, the WHO/UNDP/World Bank Special Programme for Research and Training in Tropical Diseases (TDR) continues to carry the major responsibility for sponsoring and coordinating the world effort. Several candidate malaria vaccines are at or near the field trial stage, and progress in schistosomiasis is also impressive.

Not surprisingly, the pressure to find an AIDS vaccine is enormous and the results of over a dozen clinical trials are eagerly awaited. Some of these trials aim to improve the immune status of people already infected with the HIV virus so as to prolong the disease-free interval (perhaps indefinitely), while others seek to protect against initial infection. While most of the funding for AIDS vaccine research comes either from national medical research funding agencies or from industry, WHO nevertheless has a large role to play in coordination and in ensuring international collaboration.

In these vaccine-related programmes, WHO's coordinating and sponsoring role is very important because the interest of the pharmaceutical industry in many of the diseases afflicting only the developing countries is limited. Thus, academic institutions and national research laboratories must carry the major burden, and WHO can help to focus these efforts on an international basis.

Patience and persistence

There is every reason to be optimistic about new and improved vaccines through modern research, but it is important to be realistic about time frames. At the scientific level, each disease poses its own problems and it is essential to find the weakest point in each pathogen so as to direct the immune attack to that spot. A major hurdle for many pathogens is their capacity for mutation and variation, which allows them to dodge away from immune defences. At the technical level, scale-up from laboratory to factory production poses its own serious challenges, and staged clinical trials – always vitally necessary – require careful design and last a frustratingly long time. Moreover, both research and development are costly.

Those of us whose main activity lies in research and research promotion see efforts like the Programme for Vaccine Development as an absolutely key component within the wider framework of the Children's Vaccine Initiative. The clamour for "relevance" and "quick fixes" can sometimes become strident, but while some new vaccines will come on stream quite soon others face formidable scientific obstacles which must be overcome with patience and persistence. Microbes and other pathogens have had eons of evolution to develop their infectious strategies. If we are to foil these through science, we must winkle them out progressively, sustained by the enormous prize at the end. Vaccines have already eliminated one scourge from the globe, namely smallpox. Eradication of measles and poliomyelitis is foreseeable. Such achievements will remain among humanity's noblest triumphs.

The Children's Vaccine Initiative represents an opportunity to maintain and enhance that tradition, and vaccine research is its underpinning. All over the world, scientists have responded to it with passion and commitment. It now deserves fitting long-term support. ■

Sir Gustav Nossal is Director of the Walter and Eliza Hall Institute of Medical Research, Post Office, Royal Melbourne Hospital, Victoria 3050, Australia.

A crisis to be overcome

Isao Arita

Experience with WHO's Smallpox Eradication Programme shows that it is possible to establish a worldwide supply mechanism for high-quality vaccines.

The Expanded Programme on Immunization (EPI) has developed an excellent vaccine delivery system at country level. In 1974, the vaccination coverage with six antigens was less than 5% in most developing countries, whereas today the coverage has reached some 80%. This achievement has resulted in a substantial reduction of the incidence of EPI diseases. However, three major problems – coping with increased demand, ensuring quality control, and introducing new vaccines – pose what amounts to a vaccine crisis.

Firstly, although the demands for vaccine have considerably increased, a global system to meet them has not been developed or is not yet well coordinated among multilateral and bilateral agencies, nongovernmental organizations, and producers in private and public sectors. World production capacity actually exceeds the demand, but it is not possible to make the vaccines fully available to the global programme except in the industrialized countries.

A good example is the current shortfall of oral poliovaccine for the global poliomyelitis eradication programme. This is caused by the change in immunization strategy, as a result of the need to cover older age groups than previously (under 12 months only) in order to stop transmission. Recent estimates show that about 1650 million doses are required each year for the global programme. This is three times higher than previous estimates. Efforts are being made to cover this increased demand, but at present we have no definite solution.

EPI has now set up time-limited programmes for the elimination of neonatal tetanus by 1995 and a 95% reduction in measles deaths, also by 1995. There is concern whether the global vaccine supply system will meet the demands required to attain these goals.

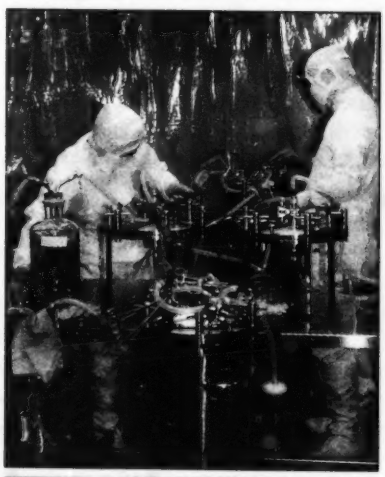
Secondly, in recent years national production lines have been increased in many developing countries, but regulatory control of the vaccines' quality has not been adequately developed. For example, among some 60 producers of tetanus toxoid throughout the world, the quality of 40 products is not known. Roughly half of the vaccines in EPI use have not been assured for quality by the independent regulatory authorities.

Thirdly, it has proved difficult to introduce new vaccines since the inception of the programme in 1974, despite great developments in vaccine research leading to, for example, hepatitis B vaccine. Even now, the latter is available in only limited quantities in the developing countries where it is most needed.

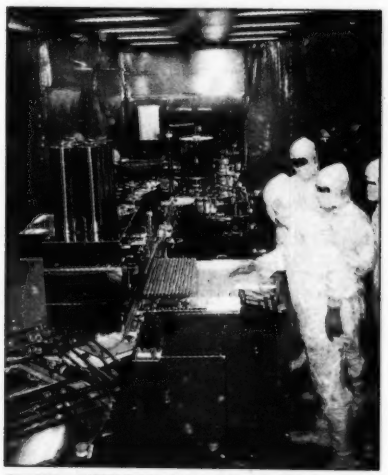
Towards self-sufficiency

The Children's Vaccine Initiative (CVI) should now seek solutions to these three important problems. Solving the first two will, I believe, pave the way for solving the last one, namely, the introduction of new vaccines, because introducing any

Towards vaccine self-sufficiency in Indonesia: examining cultured cells.



Filtration of poliovaccine.



An expert discusses the preparation of measles vaccine with laboratory workers.

new vaccine requires an efficient mechanism for vaccine supply and quality control.

In the last two decades, several countries with a population over 50 million have initiated vaccine self-sufficiency programmes. CVI has decided to promote this through its Vaccine Independence Initiative. The plan includes: full production of EPI vaccines; production sharing; quality-control sharing; and a revolving fund and other support for vaccine procurement. Production sharing means sharing the bulk of output with partner laboratories. Quality-control sharing means sharing complicated tests with a partner laboratory.

Some 11 countries were tentatively selected for initial feasibility studies in the development of full production and quality control of six antigens and/or production sharing. They are – in order of infant population size of individual countries – India, China, Indonesia, Pakistan, Brazil, Bangladesh, Mexico, Iran, Viet Nam, Egypt and Thailand. These eleven countries easily account for more than half of the world total of 140 million infants. Hence, if the initiative succeeds, the problem of vaccine supply should be much reduced.

The feasibility studies will be based on criteria such as reasonably developed infrastructure of related industries, large market size, production experience, possible quality control, possible availability of donors, and political commitment. That last criterion, namely political commitment on the part of recipient and donor countries, is of particular importance.

Other countries may be added and some may drop out in the course of this investigation. The whole undertaking requires a great deal of funding, particularly from bilateral donors, as well as expertise from producers in industrialized countries. Therefore, it is important to involve the possible donor's participation during the earliest phase of feasibility studies.

CVI teams have already visited China and Viet Nam to review their poliovaccine quality, and joint teams are being sent to Bangladesh, Brazil, Egypt, Mexico, Viet Nam (a second visit), and elsewhere to make a preliminary assessment of feasibility according to the established criteria. The Pan American Health Organization (PAHO) has already put into effect this vaccine independence initiative, including the use of revolving funds.

Ensuring quality and supplies

To put the problems in perspective, I can compare the situation of the EPI vaccine programme to that of WHO's Smallpox Eradication Programme, with which I was involved. In the smallpox programme, the assurance of vaccine supply in quantity and quality was the most critical problem during the first four years of the programme (1967–70).

The first development was the introduction of international quality control. Initially only 30% of the smallpox vaccine batches met WHO requirements. The system finally ensured that more than 80% of the production batches met WHO requirements. The second development was the establishment of a global vaccine supply system whereby smallpox-endemic countries with large populations became self-sufficient, with vaccine supply meeting their national vaccine demand. At least two-thirds of the vaccines were met by local production lines.

Thus, it was possible for the Smallpox Eradication Programme to establish a worldwide supply mechanism of the vaccine with strong international quality control because of full support from the international community as well as from national health authorities. Although concerned with only one freeze-dried vaccine, we have this past experience to show that our aims with EPI vaccines can be achieved.

There will be a great deal of work still to do. Technology transfer, for instance, will pose many problems and it is urgent to attract the interest of donors. Above all, it is of vital importance to have firm leadership with an effective structure in order to proceed with the plan. ■

Dr Isao Arita is Chairman of the CVI Task Force for Situation Analysis and Global Vaccine Supply, and Vice-Chairman of the Agency for Cooperation in International Health (ACIH), 4–11–1 Higashi-machi, Kumamoto City 862, Japan.

The poliomyelitis immunization strategy now includes older children.

Third World vaccine production

Hermann G. Schatzmayr

Vaccine producers in the developing countries have an important role to play in supplying high-quality products, and their efforts need to be supported by both the public and private sectors.

Each year, some 140 million children, 95% of whom live in developing countries, need protection by vaccination.

Vaccination is undoubtedly the most effective measure against infectious diseases, particularly if we consider its cost against the cost of treating the clinical case, not to mention the loss through death of the patient.

The increasing commitment of the international health community to extend vaccination to all the babies born in the world each year (currently 140 million) has been remarkable during the last decade. This trend underlines the responsibility of governments and the need for international support to the developing countries, where about 95% of the newborn babies are found, and indeed where important improvements in vaccine development have been discovered.

Ever since the last century, the public sector has been involved in the production of vaccines, starting with smallpox and rabies, then followed by the development and production of DPT (diphtheria – pertussis – tetanus) vaccine and BCG (for preventing tuberculosis). Today, government production is responsible for at least 60% of the DPT vaccine available (although quality standards may vary) as well as significant amounts of BCG and yellow fever vaccines. The public sector often produces vaccines by traditional methods, and clearly the introduction of modern techniques is essential.

As for the price of vaccines, at present the private sector sells them at higher prices to industrialized countries and lower prices to developing countries (through such international bodies as UNICEF and WHO). This mechanism might be difficult to maintain over a long time considering the increased demand for vaccines in the developing countries and the rising costs of production.

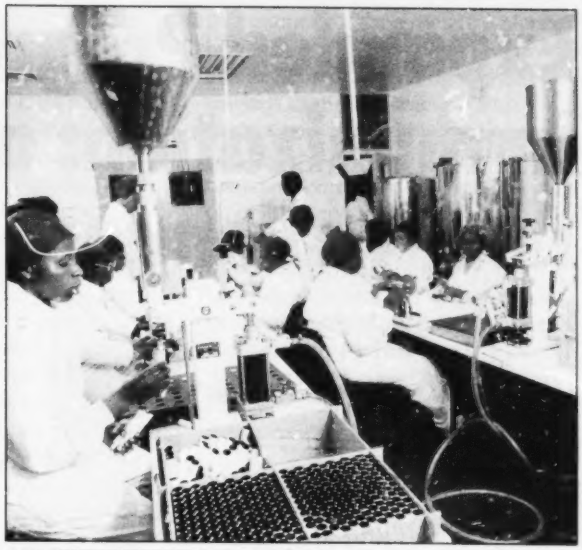
All these facts point to the need to strengthen the public sector as a world vaccine producer, in both industrialized and developing countries, with the former acting mainly as technology donors to the less developed areas.

Quality control

To ensure the production of good quality vaccines in non-industrialized areas on a regional basis, the following aspects are crucial.

- Definition by national authorities of the vaccination goals to be achieved, in order to guarantee a market for the products.
- Concentration of the production in a few larger countries, or in those with most experience in vaccine preparation. The existence of a large number of producers around the world, as we observe now with DPT vaccine, entails difficulties in quality control, which is an essential step towards improving the protection of the vaccinated population.
- Close interaction of the public institutions involved in the project, in each of the developing countries which are able to produce vaccines. This is to avoid duplication of activities and ensure that the best possible technologies are being used and are adapted, when necessary, to local conditions.
- Establishment of a national laboratory to control the quality of the vaccines, supported by national authorities and international institutions.

Vaccine production in the Philippines.



Quality control of vaccines being carried out in a laboratory in Lesotho.

The control of vaccines may be a difficult task, and is normally achieved only after years of preparation of human resources and investments in building construction and purchase of equipments. Whenever possible, the expertise of one country in vaccine control should be shared by others that are geographically close or share common cultural links.

The existence of more than one laboratory for quality control in the same country should be strictly avoided, since any conflicting results which might arise could destroy the mutual confidence between producers and controllers. International laboratories responsible for vaccine control should be able to collaborate with the regional control laboratories, through exchange of information and experts, training courses and similar activities. The control laboratories should be regularly visited by international experts in order to maintain high standards of control procedures.

The transfer to developing countries of technology in the production of biologicals needs to be stimulated by both government and private organizations. Outstanding technologies are available from public institutions in various developed countries, and have already been made available to less-industrialized regions. Expanding these activities is likely to prove both possible and highly effective. Contracts for vaccine production have been signed between private companies in the developed world and institutions outside those regions. These mechanisms too should be stimulated, and more experience is needed in the developing countries in drawing up such contracts, especi .lly when the public sector is involved as a recipient of the technology.

Private expertise

The private sector has been responsible for developing new vaccines such as hepatitis B recombinant vaccine, using molecular biology. Under this technology the same organism used for beer production (*S. cerevisae*) is induced to produce in large tanks those parts of the virus necessary for immunization. The private sector has much more experience in the large-scale production of biologicals, including rapid response to emergency situations, than the public sector. Consequently, the expertise of the private sector, as owners of the new and indispensable technologies, is an essential part of the whole system of vaccine supply for the world.

However, there is a clear tendency for producers in the private sector to decline in numbers. In the USA, for instance, only three vaccine producers out of the 20 existing in the 1960s are still operating. This decline has been due to different factors; essentially the high industrial costs and legal problems deterred many from continuing their activities.

Efforts are being made at present to give each child as many different vaccines as possible at the time of each vaccination intervention in the health care centres. This can be achieved by combining various products in the same syringe, but it calls for a lot of effort and much cooperative research between the producers in the private sector and the health authorities.

In summary, vaccine producers in developing countries have an important role to play in supplying high-quality products, and they need to be supported in their efforts by the mechanisms suggested here. If the world's children are to receive all the vaccines they need in the coming years, an adequate balance will have to be struck between the improved participation of the public sector in developing countries, the participation of government institutions in the industrialized areas, and the industrial capacity of the private sector. ■

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Expanded Programme on Immunization: achievements and challenges

Each dollar invested in immunization will result in an even greater return in prevented disability and death, and avoided medical care costs. Further expansion of immunization services is one of the best bargains available for primary health care and national development.

Immunizing pregnant women is important; it will protect their babies from neonatal tetanus.

For the Expanded Programme on Immunization (EPI) the past decade has been one of building national immunization systems, with the primary focus on developing countries and with the primary objective of expanding coverage as quickly as possible. National programmes, backed by an impressive coalition of national and international partners, have now for the most part succeeded in establishing systems that reach the majority of children attaining one year of age with a protective course of immunizations.

The global achievement of the 1990 target of 80% immunization coverage among infants worldwide with BCG and measles vaccines, and with the third dose of DPT (diphtheria – pertussis – tetanus) and oral poliovirus vaccines, represented a milestone on the way to universal childhood immunization. This progress in global immunization is directly attributable to the efforts of national governments, WHO, the United Nations Children's Fund (UNICEF) and other bodies of the United Nations system, bilateral development agencies, and nongovernmental organizations such as Rotary International. Developing the capacity to achieve these levels of coverage of infants was a major public health triumph for the decade of the 1980s.

Global statistics, however, mask disparities among regions, countries, states or provinces, and districts. Differences in immunization coverage levels reflect, in part, the varied development of the primary health care infrastructure, and are one of the measures of the degree of equity and social justice that communities have achieved. The much lower coverage of 42% reported for tetanus toxoid among pregnant women in developing countries to protect their newborn babies from neonatal tetanus serves as a reminder that neonatal tetanus was the "forgotten" vaccine-preventable disease of the last decade, which was partly due to the fact that efforts to prevent it were directed at a target population different from infants.

Coverage must be increased

At current levels of immunization coverage, it is estimated that immunization programmes prevent each year some 2.9 million deaths from measles, neonatal tetanus and pertussis, as well as some 530 000 cases of paralytic poliomyelitis. The occurrence each year of an estimated 2.1 million deaths from these same diseases, as well as 120 000 cases of paralytic poliomyelitis, underlines the urgent need to continue raising immunization coverage levels and to focus on control of the target diseases. The 1 to 2 million deaths attributable to hepatitis B infection highlight the importance of adding new vaccines.

The success of the global immunization initiative has been remarkable, but there is no room for complacency. The sustainability of immunization services in many developing countries remains fragile, a symptom in part of a poorly developed health infrastructure. In the 1990s, EPI will have as a central task, along with other WHO programmes, to strengthen the health care infrastructure. This will be pursued both by working for the better integration of immunization with other primary health care services and by further improving immunization services themselves – paying special attention to "reaching the unreached", that segment of each society which bears the highest burden of disease and disability. Integration will be carried out through training and evaluation linked with other maternal and child health programmes, and by the active promotion through EPI of other interventions such as micronutrient supplementation. The major strategy for improving immunization services themselves is to move from a focus on coverage to a focus on impact. This is where the disease control initiatives concerning neonatal tetanus, measles and poliomyelitis play a critical role.

The World Summit for Children, by endorsing the joint WHO/UNICEF health goals, spelled out the major

Diphtheria – a killer disease of children – is preventable through vaccination.

Tetanus – sometimes known as lockjaw – is another preventable disease of childhood.

One shot only will save from tetanus

Tetanus is still a killer in the developing world, particularly among newborn babies. In the past it was commonly known as lockjaw because of the painful spasm of the jaw muscles which is a characteristic early symptom of the disease. Young girls and pregnant women who are immunized against this disease under the Expanded Programme on Immunization receive three doses of vaccines at intervals. However, current research suggests that it should soon be possible to fully immunize everyone with one dose only.

The Product Development Group on Single-Dose Tetanus Toxoid Vaccine, established by the CVI, is committed to finding a technology applicable to tetanus immunization, and especially for the reduction of neonatal tetanus, that would prove just as efficient as the conventional three-dose product. It should be safe, convenient to use, and as stable as the conventional vaccine.

The main line of research is to develop a controlled-release vaccine by injection of the tetanus toxoid encapsulated in microspheres prepared from copolymers of lactic and glycolic acids. This research is being carried out under the auspices of the WHO/UNDP Programme for Vaccine Development (PVD) and the above-mentioned Product Development Group to assess whether this goal can be achieved using this technology. Other lines of study – like the possibility of obtaining preparations suitable for oral delivery including the alternative approach using salmonella bacteria as vectors for the tetanus toxoid – will continue to be assessed by the PVD.

Meanwhile, the Product Development Group will try to develop appropriate partnerships for this new technology with vaccine manufacturers.

challenges for immunization programmes in the 1990s as follows:

- maintenance of a high level of immunization coverage (at least 90% of children under one year of age by the year 2000) against diphtheria, pertussis, tetanus, measles, poliomyelitis and tuberculosis, and against tetanus for women of child-bearing age;
- global eradication of poliomyelitis by the year 2000;
- elimination of neonatal tetanus by 1995; and
- by 1995, reduction by 95% of measles deaths and reduction by 90% of measles cases compared to pre-immunization levels, as a major step towards the global eradication of measles in the future.

Improving immunization coverage beyond 80% and achieving the disease control targets will be more difficult than reaching the 80% immunization coverage target for 1990, since efforts will need to be targeted towards high-risk, and possibly difficult to reach, populations. This means that immunization programme managers will have to improve the information system so as to identify pockets of unimmunized children and areas of continued disease transmission as well as expend greater efforts to determine which aspects of the programme need to be enhanced to reach them. Increased resources to intensify the delivery system and strengthen capacities to respond to outbreaks will be required.

Quiet revolution

The past 15 years have witnessed a "quiet revolution" in health. Immunization programmes have been a prime mover in the development of an increasingly effective health infrastructure that is now making some 500 million contacts with infants and mothers each year. The challenges ahead lie in tapping the full potential of these contacts in the decade of the 1990s to control an expanding number of target diseases and help provide increasingly complete primary health care. The global coalition built around immunization programmes will serve to further improve immunization and disease control activities, and will act as a catalyst for building more comprehensive health services in developing countries. This health infrastructure contributes, in turn, to national development.

Quite apart from the important humanitarian reasons for immunizing, the investment in immunization services makes sound economic as well as epidemiological and political sense. Disease prevention through immunization reduces not only deaths, but also the need for expensive curative and rehabilitative care. In the situation of disease eradication, as with the poliomyelitis eradication initiative (see opposite page), there will be the ever-accumulating benefits of being able to stop all activities relating to the prevention and treatment of the disease.

Immunization, in both industrialized and developing countries, will continue to be an important element of national health programmes as new and improved vaccines become available. Each dollar invested will result in an even greater return in prevented disability and death, and avoided medical care costs.

To these direct benefits are added important indirect benefits: immunization provides a means of helping to break the vicious cycle of high infant and childhood mortality rates. By permitting more of a family's children to survive, it reduces the number of births desired by a family which, in turn, reduces maternal, infant and child mortality rates. In this way it acts in strong synergy with family planning activities, and makes the further expansion of immunization services one of the best bargains available for primary health care and national development.

Immunization programmes face exciting challenges during the present decade. The continued commitment of governments and the international community to meet these challenges will move us all closer to the ultimate vision of a world free of suffering, disability and death due to vaccine preventable diseases. ■

Contributed by Dr Robert J. Kim-Farley, Director of the Expanded Programme on Immunization, and his team at WHO headquarters, 1211 Geneva 27, Switzerland.

Immunization programmes are best managed when they are carried out within the primary health care services.

An informed community will ensure that no child is left unprotected.

Polio eradication is in sight

Harry Hull

A cooperative, global effort is needed to go those last steps that are always the hardest part of the journey. How can we afford to stop when we have come so far?

More than 100 000 children are still left paralysed every year by poliomyelitis.

Poliomyelitis was a very real part of my childhood in the suburbs of Chicago, USA. I remember, as a three-year-old, watching my mother being carried on a stretcher down the stairs of our home to a waiting ambulance when she contracted polio in 1952. Though her paralysis was mild, with virtually complete recovery, many others were not so fortunate. One of my neighbours struggled on to the school bus every morning, to sit in the front seat – her withered legs in calipers, her crutches leaning against the window. Many more were confined to iron lungs, their breathing sustained by a pulsating, electrically-generated vacuum. Virtually every summer there was a polio panic – swimming pools and theatres closed, public events cancelled – as parents lived in terror that their child might be the next victim.

All that ended in 1955 with Dr Jonas Salk's dramatic discovery of the first poliovirus vaccine. My brothers and sister and I, along with millions of other children, were rushed to family doctors to receive injections of the killed poliovaccine. The disease virtually disappeared from the USA, Canada, Europe and the industrialized countries of the Pacific following the introduction of the Sabin live, oral poliovaccine (OPV) in the 1960s.

Today, I am one member of a team working within WHO's Expanded Programme on Immunization (EPI) to eradicate poliomyelitis from the world. Dr Nicholas Ward, who heads the eradication team at WHO headquarters, says that one major obstacle facing the team is that polio is perceived as a problem that has been solved. "It was only in the 1970s that lameness surveys in Africa proved that paralytic polio occurred in the developing world at rates equal to, or higher than, those in the industrialized world prior to the advent of vaccination." Before then, it had been accepted that the infection in developing countries was associated with lower rates of paralysis. "Even today," he says, "many of our acquaintances believe that polio has vanished." WHO estimated that, as recently as 1980, more than 400 000 children were paralysed each year. Outbreaks in 1991 and 1992 in Bulgaria, Jordan and the Netherlands – all of which had been free from the disease for years – emphasize the

continuing risk of polio for all countries of the world.

WHO's Expanded Programme on Immunization was created in 1974 as the successor to WHO's Smallpox Eradication Programme. EPI's goal was to provide a basic course of immunizations, including three doses of OPV, to all children. Its success has now set the stage for the global eradication of poliomyelitis. As a result of the universal childhood immunization initiative, 84% of infants born in 1990 were immunized against poliomyelitis. WHO estimates that, as a result, only 127 000 cases of paralytic poliomyelitis occurred worldwide in 1991. (In fact, only 14 128 cases were reported to WHO). Dr Robert Kim-Farley, Director of EPI, cautions against complacency. "Eradication of polio means that we seek to totally destroy the virus that causes polio. With that goal in mind, the occurrence of even a single case of poliomyelitis is unacceptable."

Before the first poliovirus vaccine in 1955, children affected by polio depended on an iron lung for their survival.

A young Greek child receives the oral poliovirus vaccine.

A disease passes into history

Five years have now passed since the World Health Assembly first proposed an initiative to eradicate poliomyelitis from the face of the earth by the year 2000. In those five years, the numbers of reported cases of acute polio have fallen from over 32 000 in 1988 to 14 128 in 1991 and to an estimated 12 000 in 1992. This 62% reduction in cases since 1988 has occurred in spite of improved case detection, although satisfaction at this downward trend must still be tempered by estimates that only 10% of actual cases are being reported.

The most striking success has been in the Western Hemisphere (covering North, Central and South America and the Caribbean) where, in spite of intensive searching, no polio case caused by wild poliovirus has been detected since September 1991.

Worldwide, WHO staff, with their colleagues from UNICEF and Rotary International, are helping countries to forecast their vaccine needs, further exploring the possibilities of local production or bottling from bulk imports. WHO places high priority on strengthening surveillance, not only for polio but also for other communicable diseases, and workshops have been conducted for staff from over 70 countries. WHO is also helping to develop a laboratory network that will support the diagnosis of suspected cases. Within each WHO Region, a number of national laboratories are attempting to isolate polioviruses from suspect cases.

Apart from the human and economic benefits of eradicating poliomyelitis, immunization with poliovaccines has a high cost-benefit. One study showed that, by 1998, the benefit of not having to treat the polio disabled will start to outweigh the costs of the vaccine and its administration. When, eventually, immunization can be stopped everywhere, the savings will be enormous, the USA alone no longer having to spend over US$ 110 million on poliomyelitis vaccine each year.

Before poliovaccines were developed, half a million children suffered from the disease each year. When the last virus is eradicated, that half million will be reduced to zero. As has occurred with smallpox, now eradicated for over 15 years, future generations will only know the disease from history.

Even the most remote areas, as shown here in Mexico, can be reached by vaccine supplies.

Smallpox showed the way

The philosophy of polio eradication is grounded in smallpox eradication, since many of the leaders of the initiative were involved in that programme. Eradication initiatives seek to improve disease surveillance so that every case of the disease is rapidly detected. Immunization is then targeted to the highest risk areas to interrupt transmission of the virus. Once global eradication has been achieved, immunization against polio will no longer be needed. Eradication is the most cost-effective and sustainable approach to disease control, according to Dr Kim-Farley. "Once polio eradication has been achieved, more than US$ 100 million will be saved each year in the USA alone for vaccine that does not have to be purchased and medical care that does not have to be provided. The increased human potential for children who are not crippled is impossible to measure."

The actual strategies used in the eradication initiative were defined in the WHO Region of the Americas under the leadership of Dr Ciro de Quadros. Beginning in 1985, he assembled a coalition of international donors to provide coordinated support to the initiative: UNICEF, USAID and Rotary International were among the leaders. National vaccination days and campaigns administering OPV to all children under five years of age served both to suppress circulation of wild polioviruses and to increase each child's individual immunity. The last case of poliomyelitis caused by a wild poliovirus in the Western Hemisphere occurred in August 1991.

These strategies are now being adopted and adapted for use elsewhere in the world. Significant progress is being made, for example, in China, where reported cases have decreased by 58% between 1989 and 1991. Potentially polio-free zones are emerging in North Africa, southern and eastern Africa, the Middle East, Europe, and the Pacific rim. Once established, these zones will be expanded to include neighbouring, polio-endemic countries.

The Indian subcontinent, where India, Pakistan and Bangladesh account for two-thirds of the reported polio cases in the world, is an important global polio reservoir, where additional progress is needed soon to reduce the risk of the disease being exported to polio-free areas. War and political instability in Europe, Asia and Africa remain significant obstacles to the global initiative.

Political will

Despite strong support from external donors, funding for much of the logistical support involved must come from in-country resources. In the programme in the Americas, the $112 million provided by external donors covered only 21% of the total cost.

But the greatest obstacle facing WHO's polio eradication initiative is one of political will. In 1988, the World Health Assembly called for the global eradication of poliomyelitis by the year 2000. More than one-third of the allotted time has passed. Although cases have decreased as a result of improved immunization coverage, the number of countries conducting specific polio eradication activities is limited. Laboratories need to be equipped and staff trained, and an estimated additional $300 million worth of OPV will be needed. Polio-endemic countries must commit themselves to allocating sufficient human and financial resources, and donor agencies and governments of industrialized countries must also commit themselves to supporting these countries.

WHO, its Member States and their financial supporters will need to focus attention on the benefits that will accrue from polio eradication – improved disease surveillance, better laboratories, cost savings to immunization programmes in every country – rather than on the difficulty and cost. A cooperative, global effort is needed to go those last steps that are always the hardest part of the journey. How can we afford to stop when we have come so far? ■

A cheerful moment for this Kenyan mother: her child is protected against polio.

Dr Harry Hull is Medical Officer with the Expanded Programme on Immunization, at WHO headquarters, 1211 Geneva 27, Switzerland.

The cost-effectiveness of immunization

Peter Cowley & Dean T. Jamison

Immunization is one of the most cost-effective of health interventions.

A World Bank review shows conclusively that immunization compares very favourably in cost-effectiveness with clinic-based and other public health initiatives in terms of "disability-adjusted life years".

Over the past four years the World Bank, with a number of collaborators, has undertaken a review of priorities in the health sector. The core of the review is a series of papers on the public health significance of major clusters of diseases in the developing world, and on the cost and effectiveness of currently available technologies for their prevention and case management. The range of diseases studied is extensive, but by no means exhaustive; the results show that cost-effectiveness measures can be potent tools for guiding the health sector on how best to allocate resources and how to determine which of many potentially important interventions should have priority.

As a first step towards setting such priorities from a cost-effectiveness viewpoint, it is necessary to attempt to assess the impact of an intervention in terms of premature mortality, disability or pain, and to weigh this impact against cost. The measure of impact used is Disability-Adjusted Life Years (DALYs), which represent the sum of the years lost from death, and from disability associated with disease and injury. Years of life lost due to premature death at a certain age x are measured by subtracting x from the expected years of life, given a life expectancy at birth of 80 years for men and 82.5 for women. Years lost due to disability are estimated in the same way as mortality, except that the total years are multiplied by a value (less than unity) assigned to the disablement according to its severity. Each of the future years which are lost or are spent disabled are discounted at a cumulative 3% rate per annum back to the present, which makes those years lost in the distant future less valuable than those lost in the near future.

The *Health sector priorities review* commissioned by the World Bank found that there was a broad range of costs associated with saving a DALY. In fact, those costs varied from under US$ 10 to over $10 000 per DALY saved. The cost-effectiveness of immunization programmes compares favourably with clinic-based programmes and other public health initiatives as expressed in dollars needed to prevent one DALY. Immunization programmes constitute more than one-third of the public health interventions examined whose cost-effectiveness can be estimated at less than $75 per DALY gained.

Immunization costs

The Expanded Programme on Immunization (EPI) on average costs $15 per fully immunized child for the "basic" package. However, these

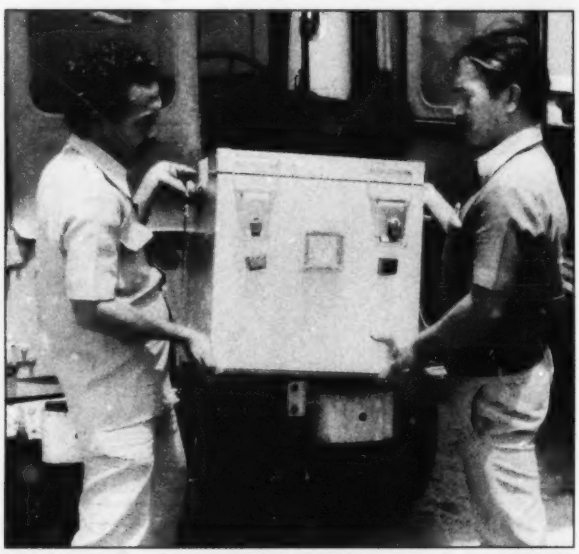
costs can vary somewhat since they depend on the infrastructure present in a country. These start-up costs often include the technology such as kerosene refrigerators needed for a cold chain in order to keep the vaccines from spoiling. The costs of the cold chain could be kept lower if only we had heat-stable vaccines.

The cost-effectiveness of an EPI-plus programme, which would include immunization with hepatitis and yellow fever vaccines in areas where these diseases are prevalent, would only raise the overall costs by some 25% if both vaccines were given, and would still lead to a cost per DALY gained well below $25. It has been suggested that early childhood immunization programmes could act as vehicles for delivering vitamin-A supplements since vitamin-A deficiency peaks in children aged 2 to 4 years, and using the EPI infrastructure would reduce costs. Furthermore, projections show the yearly costs of vitamin-A supplementation and the cost per DALY gained to be similar to those of one "basic" EPI package.

The geographical distribution of the target population will also affect the cost-effectiveness, as a widely scattered population will require more resources in order for everyone to be reached by an immunization programme. However, these populations often have poor health indicators, including high mortality rates from vaccine-preventable diseases. Thus, any increased resources used for such activities as immunization campaigns can be balanced by increased gains against vaccine-preventable diseases.

The cost-effectiveness of an immunization programme will depend not only on the resource costs due to

Maintaining the vaccine at the right temperature up to the point of delivery . . .



. . . requires funds and good organization.

A heat-resistant poliomyelitis vaccine

The vaccine currently used to protect children from poliomyelitis soon loses its potency when exposed to excessive heat, as may readily occur in many tropical countries. The Expanded Programme on Immunization overcame this difficulty by keeping the vaccine at the required temperature from the moment it is manufactured up to the point where it is administered, using an uninterrupted "cold-chain" of different types of refrigerators and finally the ice-box that the community health worker carries on his or her bicycle. Having a heat-resistant product would considerably simplify the delivery of the poliovaccine, and the saving in cost and improvement in logistics would bring poliomyelitis eradication even closer.

The Product Development Group on Thermostable Oral Poliovaccine has been charged by the CVI with developing vaccines capable of withstanding exposure to a temperature of 45°C for at least seven days without losing their potency, and ensuring their industrial manufacture.

One line of research has already identified several antiviral compounds which can stabilize the antigenic structure of poliovirus for seven days at 42°C, or for three days at 45°C. Another stabilizing system was able to maintain the virus infectivity for seven days at 37°C – still short of the target.

A second approach involving drying of the poliovirus in the presence of a novel carbohydrate, trehalose, produces a vaccine which is completely stable when dried. However, research to overcome the large drop in virus infectivity and vaccine potency is being actively pursued.

vaccine delivery but also on the costs of the vaccine itself and those costs associated with surveillance of the targeted disease in order to monitor the programme's effectiveness. The costs of the vaccine itself are not overwhelming. The costs of surveillance may vary widely, depending on the epidemiology infrastructure present in the country and the strength of communication between surveillance outposts.

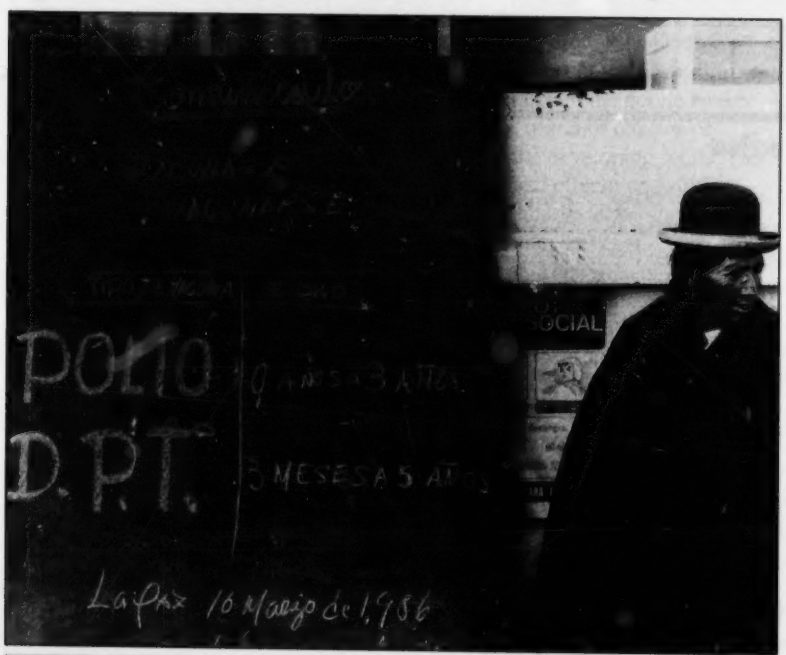
Future resources saved

Immunization becomes even more cost-effective in environments where the average annual risk of infection of the targeted disease is high. Even in environments where the average annual risk of infection is low, the cost-effectiveness of immunization may still be apparent; as the average annual risk of infection of the vaccine-preventable disease decreases, the cost of preventing one DALY increases, since the vaccine will be given to large portions of the population who will never have the disease. Although the average annual risk of infection of poliomyelitis is low in the Americas, immunization is still beneficial because it increases the chances of eradication and prefigures the future resources saved in not having to immunize against an already eradicated disease.

Cost-effectiveness can be used to help determine the timing of administration and type of vaccine used in a programme. For instance, in areas where there is a measles epidemic, infants are often vaccinated at as early an age as six months, although the efficacy rate of the measles vaccine at six months is less than that at nine months and often necessitates a two-dose schedule for measles vaccination – one at six months and one at nine months. Nonetheless, this two-dose schedule can still be cost-effective considering the greater proportion of measles cases averted.

Cost-effectiveness data have indicated that the combining of vaccines into a "super vaccine" given at birth would be extremely beneficial. In fact, this is one of the prime directives of the Children's Vaccine Initiative (CVI). A reduced number of contacts is crucial, since the majority of the costs from any immunization programme stem from the delivery of the vaccine. A reduced number of contacts will also lead to higher coverage rates. Finally, the CVI itself is using cost-effectiveness data to help determine the direction of short- to medium-term research goals by assisting in identifying research costs and potential cost-effective dosing schedules as well as inexpensive heat-stable vaccines. ■

Reaching scattered communities inevitably raises the cost of immunization campaigns.



Timing vaccination campaigns correctly makes them more effective – and also saves money.

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Partners for progress

Richard Arnold

The Expanded Programme on Immunization has achieved dramatic results in reducing the toll of its target diseases. Advances in vaccine technology in recent years now offer prospects for practical approaches to extending the prevention of several of the most serious diseases which continue to kill and incapacitate many of the world's children.

On one hand, improved vaccines may be developed to overcome the difficulties of achieving full cover against some of the EPI diseases themselves. Those difficulties may be due to problems of cold-chain maintenance or to the remoteness of some populations, with consequent limited access by health workers. On the other hand, diseases now not covered by EPI could be attacked with new vaccines. But there is a long road to travel between a technical concept and the completion of a successful vaccination campaign. The technical, logistic, economic and sociological obstacles will have to be overcome. This will involve commitment and action by many parties working towards a common objective.

It is for this reason that the Children's Vaccine Initiative (CVI) has been established. The founding agencies, other donors, academic scientists and their institutions, public health authorities and the enterprises which will develop and eventually manufacture the vaccines must all play their part if the effort is to succeed. The vaccine industry has already shown itself very ready to support the Initiative.

A Brazilian scientist manipulating the malaria parasite in order to obtain antigens for vaccine research.

The vaccine industry has already shown itself very ready to support the Children's Vaccine Initiative. All the prerequisites exist for close collaboration between the industry, governments and international agencies.

Prototype vaccine

The general availability and use of a new or improved vaccine involves a number of steps. Establishing technical feasibility as a first step means proving that a prototype vaccine made in a laboratory can produce immunity in an animal model. Developing a new vaccine is very different from developing a new synthetic drug, where the process starts with the creation of a unique new chemical entity which is the key innovative step, even though the risks and costs are mainly encountered during the lengthy development process before marketing. Vaccines, on the other hand, may be of many types. They may be made from a live but attenuated pathogen, or from a killed pathogen, or they may be made from a fragment of the pathogen or by modifying other organisms involving the use of recombinant techniques. Adjuvants or special formulations may be needed in order for them to be effective. The technology involved may require the use, in part or extensively, of innovative techniques used for other products in achieving the prototype vaccine. Further technologies may be involved when production of the laboratory vaccine has to be scaled up to permit general use.

As in all other aspects of the pharmaceutical field, industrial vaccine research and development can only be undertaken with the safeguard which patents provide for the heavy investment required. In contrast to the conventional pharmaceutical field

A better measles vaccine

Despite the high coverage with current vaccines, measles continues to exact a tremendous toll on the lives of small children. Even with global vaccine coverage running at around 78%, nearly 1.5 million children continue to die from the disease each year.

At present, measles immunization in industrialized countries is given at the age of 12–15 months, so that the early immunity acquired from the mother does not interfere with the action of the vaccine. Unfortunately, in developing countries where measles transmission can be very intense and the risk of infection is generally greater than in developed countries, the waning of maternal-acquired immunity can expose children to infection long before their first birthday. WHO has therefore recommended that measles vaccinations in developing countries should be administered at nine months.

A measles vaccine that could be effective between the ages of two and six months would be most valuable. It would fill the "gap" that often occurs after the loss of maternal-acquired immunity, and would enable this vaccine to be included in the existing schedules of the Expanded Programme on Immunization.

An ideal measles vaccine should be safe, and should induce lifelong protective immunity in almost 100% of recipients with a single dose administered shortly after birth. It should also be compatible with other antigens dispensed at the same time, provoke mucosal immunity, interrupt wild measles transmission, retain its potency even at 45°C for seven days, and not be much more expensive than the current vaccine.

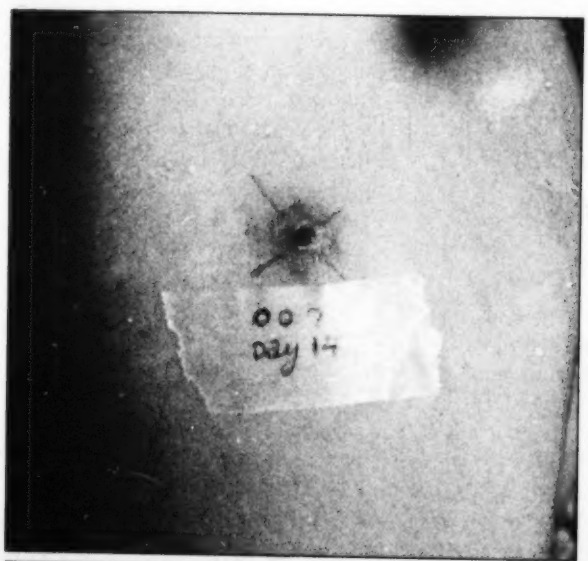
In supporting the work already carried out by WHO, the CVI has established a Product Development Group on Improved Measles Vaccine, which is to examine the current measles situation and problems with control, including vaccine coverage and vaccine failure. It has received a broad mandate to consider all promising candidate vaccines against measles.

however, where the main concern is a new chemical entity, patenting of vaccines is likely to be a much more complex issue which may require licence agreements with other innovators.

Once the laboratory activity of a vaccine has been demonstrated, its safety, efficacy and suitability for use in humans has to be established. Ways to recognize quality standards and to make it on the scale needed, at an acceptable cost, must be found. Many questions must be answered. What is the level of immunity and for what period does it last? How many and what doses have to be given? What side-effects may be produced? How severe and how common are the side-effects? These are questions which only extensive clinical trials can reveal, and such trials will involve studies in many countries with volunteers from many different types of population, over several years.

While clinical trials are in progress, assuming that they show promise, work will be done to establish a method of producing the vaccine to consistent quality standards and as economically as possible. Whether or not the vaccine can be made in existing or expanded plants or whether a new plant will be required is a fundamental question, to which the answer will also depend on an assessment of the likely demand.

The world has come to expect not only more advanced vaccines but vaccines that are safer and of reliable quality. For many years the commonly used vaccines were available at a few



Clinical trials of a vaccine against leishmaniasis.

Improved vaccines in the future will make measles cases like this a rare sight.

cents a dose. One of the consequences of low prices and monopoly purchasers in the public sector has been the disappearance from the market of many producers who were unable to obtain a return on their business. While the tendering system may produce the lowest prices for the common vaccines, the situation for a manufacturer who may get all the business one year and none the next is unsupportable. Contraction of the manufacturing sector, the high costs of assuring today's quality standards, the costs and risks of research as well as the liability risks in the market have inevitably resulted in higher prices for vaccines than in the past.

New vaccines

New vaccines in the future can never cost a few cents a dose as in the past, and this is an aspect with which CVI and its supporters must come to terms. So too must countries, since there are already signs that the ability and willingness of donors to assure supplies to developing countries are limited in both time and scope. Nevertheless, even at realistic and fair prices the economic as well as the social and humanitarian benefits of vaccination with new and improved vaccines will be seen to far outweigh the costs.

Several vaccine developers and producers are currently working with CVI on the projects already chosen. At present, collaboration involves the earlier stages of technical development, but this will evolve as the projects expand. The CVI will only be considered to have succeeded if the vaccines which emerge from the development process are extensively used in vaccination campaigns among the world's children at risk. The vaccines must meet internationally recognized standards of safety, quality and efficacy. They must be affordable in the sense that governments and agencies buy them, and they must yield a reasonable financial return to enable the manufacturer to make them. It seems likely that – for established manufacturers and especially the international research-based manufacturers – the most rational form of collaboration will usually involve both development and production of the vaccine.

There are many variations of collaborative arrangements. At one end of the spectrum the achievement of a project may involve collaboration with a series of units or organizations, each taking on a limited task; for example, one may produce and test an experimental vaccine while others will be concerned with developing a production process or with the conduct of extensive clinical trials. At the other extreme, just one collaborator may undertake all stages of development as well as obtaining regulatory approval and finally producing the vaccine on a commercial scale. Whatever the approach adopted, however, the arrangements must be equitable to all parties if it is going to succeed. Commercial organizations must be able to meet reasonable expectations of return on investment to enable the business to continue and to satisfy the expectations of their shareholders. Where the investment may be needed to build or extend production and quality control facilities, all will depend on the extent to which supplies are taken up by purchasers. Funders – whether governments, international agencies or donors – will expect safeguards against paying for tasks not properly undertaken or being charged unreasonable prices.

It is certainly not easy to devise arrangements which meet all these demands. But the prerequisites exist. All the parties, including the vaccine industry, want the Initiative to succeed and all the parties believe that it will. ■

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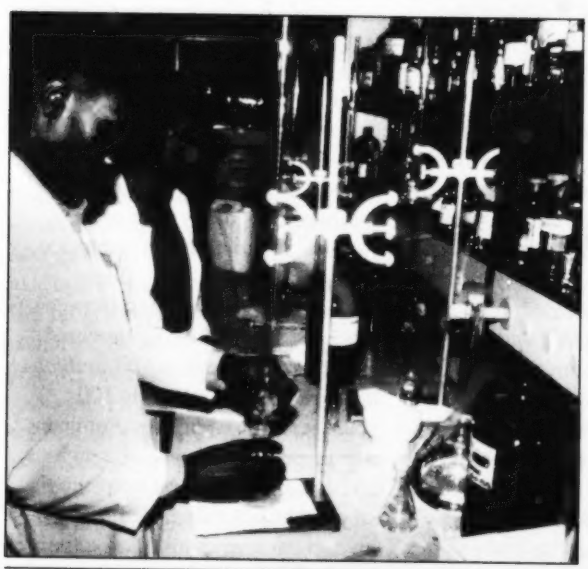


Laboratory control is vital . . .

The promise of CVI

Terrel M. Hill

UNICEF is strongly committed both to the continued success of the Expanded Programme on Immunization and to the Children's Vaccine Initiative, with its goal of creating new, improved and affordable vaccines for the developing world.

A child is born in a remote village, miles away from the nearest health facility, somewhere in Africa or Asia. This infant, like the other 140 million born this year, is highly vulnerable to a series of infectious diseases, yet these can be prevented by the miracle of vaccines.

First comes the risk of acquiring neonatal tetanus at birth, but the child can be protected against this by immunizing the mother before the child is born. Poliomyelitis and BCG vaccines are given together shortly after birth, followed by three doses of diphtheria, whooping cough and tetanus (DPT) and poliomyelitis vaccines at 6, 10 and 14 weeks. Measles, the greatest killer, cannot strike at birth because of transferred protection from the mother; however, after several months this protection wanes, and the measles vaccine needs to be given at nine months of age. Thus, the infant must be contacted by the health worker on five occasions during the first year of life.

Reaching 140 million children worldwide with potent vaccines five times during their first year of life is one of the greatest public health challenges (and achievements!) of our time. The vaccines must be protected from heat on the long road from the manufacturer right through to the village or immunization site by means of an extensive cold chain of refrigerators, freezers and cold boxes. This journey may be compared to the challenge of keeping cold an ice-cream cone purchased in Paris for consumption by a child in north-eastern Laos.

The global immunization programme (EPI), which was initiated in 1974, has made giant steps towards universally administering vaccines to the children of the world. By 1990, more than 100 million children (80%) were receiving their full series of infant vaccines by their first birthday. These coverage levels have largely been maintained through 1991. This has resulted in more than three million deaths from the six EPI diseases being averted every year.

UNICEF's role

UNICEF, the UN Children's Fund, has strongly supported the EPI since the early 1980s by providing cold chain, sterilization and injection equipment, funds for training of workers, monitoring and evaluation, and – most significantly – high quality, low-cost vaccines. Between 1982 and 1992, UNICEF procured and shipped more than *6100 million doses* of vaccines to nearly 100 countries; it also played a prominent role in mobilizing political, religious and community leaders to ensure that all children are immunized. Total investment in immunization activities by UNICEF over the past ten years has exceeded US$ 600 million, and

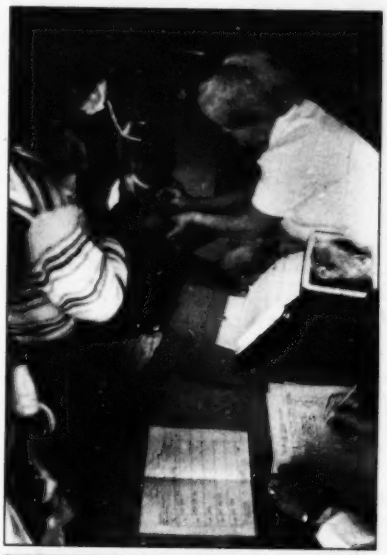
UNICEF is highly committed to the continued success of the EPI. It views immunization as a key activity or building block to enhance the development of systems capable of delivering a package of basic maternal and child health interventions universally.

The Children's Vaccine Initiative (CVI), as described in other articles in this issue, offers a promise of making the task of reaching infants easier and more efficient. The experience of the initial two years of the CVI has demonstrated that the successful development of new and improved vaccines is not merely a high-technology research project, but is a stepwise process and should be built upon the vaccines currently in use in the global immunization programme. Cost and quality of vaccines have become the two most critical issues as demand has increased, prices from international suppliers have escalated and the effectiveness of vaccines produced in some developing countries remains uncertain. Consequently the CVI will continue to develop, support and facilitate progress along two parallel tracks: building capacity and systems to ensure high quality, affordable vaccines for the EPI programme in developing countries; and promoting and coordinating research and development for new and improved vaccines. While participating in the priority setting and overall management of the CVI, UNICEF will focus its energies and resources upon the first set of activities.

During the past decade UNICEF, WHO, Rotary International, bilateral donors and several developing countries were successful in providing adequate quantities of high quality vaccines to meet the requirements of EPI programmes in developing countries. However, during the past year the provision of adequate vaccines to meet the disease eradication goals and the continued expansion of EPI have been put in question by three separate factors: higher prices, increasing volume requirements, and a shrinking resource base.

A general strategy

A task force organized by the CVI has initiated an analysis of the global vaccine situation. Preliminary data show that more than half of the vaccines used in developing countries are produced domestically. The task force developed a general strategy for assuring vaccines for developing countries which is based on three criteria: population, wealth, and technical capacity. The largest countries, which have adequate technical capacity, will be supported in producing vaccines while smaller countries will be supported in procuring vaccines. Clearly the richer countries should be completely independent in filling their vaccine needs. Middle-income countries will receive support to become independent in vaccine production or procurement. The poorest countries will continue to rely on donations for the next several years, although all countries are encouraged to provide at least a proportion of the resources needed for vaccines. The elaboration and putting into practice of this general strategy has already started. A more detailed survey of projected vaccine requirements and use, the source of vaccines used (local production or imported), and the sources of funding for vaccines is under way.



Vaccination forms one of the keystones of maternal and child care.

Teams of experts in vaccine production and quality control, as well as vaccine demand, economics and management, are visiting those countries which will be relied upon for domestic production. The teams have visited Bangladesh, China, Egypt and Viet Nam, and are visiting Brazil, India, Indonesia, Mexico, Pakistan and the Philippines during the first half of 1993. The teams assess both quality control and production capacity, in order to recommend a plan for increasing production levels to meet national requirements and to ensure that the vaccines meet WHO quality requirements. Specific proposals for donor support for each country will then be submitted for funding by interested donors. These activities are being carried out jointly by two specifically designated task forces, with operational support provided by both UNICEF and WHO.

CVI is implementing a programme called the Vaccine Independence Initiative, which assists developing countries to procure vaccines through the UNICEF system, and to pay for the vaccines either in local or hard currencies. This scheme has been implemented successfully in Morocco in collaboration with the United States Agency for International Development (USAID). Negotiations are under way in several other countries with the hope of having as many as ten countries fully operational by the end of 1993.

The CVI provides an excellent forum for multi-agency collaboration to tackle the full range of vaccine issues. UNICEF will continue to work with CVI partners so as to ensure that adequate, high quality, affordable vaccines reach the 140 million infants born every year, especially those born in remote villages in the developing world. ■

Dr Terrel M. Hill is Senior Health Advisor with the United Nations Children's Fund, UNICEF House, 3 United Nations Plaza, New York, N.Y. 10017, USA.

WHO in action

Empowering the mental patient

José Manoel Bertolote

"The one who has the key has the power." That is how many patients in mental hospitals refer to the balance of power between patients and care-givers, particularly psychiatrists. It would be preferable if we could say "used to refer to", but unfortunately in some places the power imbalance still exists. However, the key is already being shared in other places.

Mental health services – like health services in general – have often been organized in relation to the needs of staff and of the services themselves. An important recent trend is the development of services built to respond to clients' needs and their problems in community living, rather than simply fitting mentally ill people into existing services.

But developing services around peoples' needs is not an easy matter. First, you must determine their opinions and wishes. Second, reorganizing services to fit their opinions and wishes may mean major changes and may threaten vested interests. Third, there is as yet little firm and scientific evidence that the benefits arising from this new approach are superior to what went before.

WHO's Mental Health Programme sees the improvement of care for the mentally ill as one of its major tasks. Over the years it has promoted the provision of mental health care through primary and general health care rather than only through highly specialized services; it has reviewed legislation concerning mental illness, and issued guidelines about revising and drafting that legislation; and it has launched programmes on the prevention of mental and neurological illnesses, and developed guidelines about their treatment.

Removing the stigma

In the late 1980s it was clear that a major new challenge was to be faced: that of ensuring that care for the chronically mentally ill is given direct attention, and that its organization becomes based on a consensus among consumers, health service staff and the community. So the WHO Mental Health Programme launched an Initiative of Support to People Disabled by Mental Illness which is intended to facilitate the dissemination of information, to governments and to professionals, about good practice in community services for people with chronic mental illness, and about new developments in the field. The Initiative seeks to reduce the disabling effects of chronic mental illness and to highlight those social and environmental barriers which might hinder treatment and rehabilitation. These barriers prolong the stigma of chronic mental illness. The Initiative also advocates consumer empowerment and consumer evaluation of mental health services.

People who use mental health services have a right to be empowered, to have access to their own medical records, and to be free of stigmatizing labels.

The following are officially participating in the various activities:

- Mental Health Services (Northern Regional Health Authority) in Townsville, Australia;
- Mental Health Services (British Columbia Ministry of Health) in Vancouver, Canada;
- Centro Studi e Ricerche Salute Mentale (Autonomous Region of Friuli Venezia-Giulia) in Trieste, Italy;
- Mental Health Unit (Highland Health Board) in Inverness, United Kingdom;
- Ministry of Health, Netherlands.

In addition, several other groups in Austria, Finland, Germany, India, Japan, Russia, Spain, Switzerland, Uruguay, USA, and Zimbabwe have been involved in some of the Initiative's activities.

The Initiative's first step was to discover what the people who use mental health services – the consumers – think about them. These consumers included those with direct experience of mental or emotional problems, and also those who had some responsibility (e.g., as relatives or friends) in caring for mentally ill or disabled people. The views and approaches of several new consumer groups which have sprung up in many countries were incorporated into the Initiative's activities, and this proved both fruitful and inspiring.

Consumer involvement

It was quickly apparent that consumer involvement in planning, development and evaluation of mental health services is necessary and useful; and that the prerequisites to an effective and equitable dialogue which will ensure consumers' involvement in decisions affecting them include:

- the right to be empowered;
- the right to representation;
- the right to have access to one's own medical records;
- the right to be free of stigmatizing labels.

Of these, empowerment was felt to be of particular importance. One consumer group from Vancouver, Canada, explained: "As the mental patients/former mental patients community is empowered, so must each individual in the group feel a sense of his or her own personal power. As in any context, it is the defenceless and the victimized who should be the facilitators of their own protection, dignity and respect. Therefore, participation in consumer groups should be exclusive to those who are or have been mental patients; only those who have suffered the stigma and the cold shoulder of the social fabric can truly claim an understanding of what their wishes and needs are.

"While the exception can always disprove the rule, generally every instance in which there is equal participation, or significant participation, by non-mental patients in such a group, the non-mental patients always end up running the show. Control and power becomes centralized in the hands of the professionals and the so-called 'normals', so that within the confines of their own group psychiatric patients become once again disempowered."

The approval by the United Nations General Assembly of Resolution 46/119 in December 1991, on the Principles for the Protection of Persons with Mental Illness and the Improvement of Mental Health Care, represents a major advance in line with the goals of the Initiative. Advocacy groups are now in a stronger position to put forward their views on consumer empowerment.

Faithful to its principles the Initiative has concentrated most of its efforts on identifying progressive services and groups that have emphasized consumer involvement; on networking with these services and groups; and on drawing attention to examples of effective interventions for the improvement of mental health care. One example: a booklet on *Schizophrenia: information for families*, produced with the collaboration of the World Schizophrenia Fellowship – a consumer association – is now being translated into some 15 languages.

A more recent project seeks to develop ways which will allow a more systematic examination of the degree of satisfaction that patients, relatives and formal care-givers derive from the services they use or provide. ■

Dr José Manoel Bertolote, Senior Medical Officer, Division of Mental Health, 1211 Geneva 27, Switzerland, acknowledges the contribution to this article by participants in the Initiative of Support to People Disabled by Mental Illness.

Creative education for the mentally handicapped in Finland (above) and at the Townsville Centre (below).

WHO on . . .

Wearing helmets

Millions of people use bicycles and motorcycles every day as an economical means of transport, as a way of taking exercise or as a sporting activity. Unfortunately, large numbers of cyclists are killed or seriously hurt each year as a result of head injuries incurred when they fall off or are hit by another cycle or motor vehicle. Many of these head injuries can be prevented or their seriousness reduced by a simple and inexpensive device – the helmet.

A worldwide strategy to promote the use of helmets has the potential to save vast numbers of lives. In the autumn of 1991, a WHO task force met to start developing such a strategy, under the leadership of the National Injury Prevention and Control Center, one of the Centers for Disease Control in Atlanta, USA, which is the WHO Collaborating Centre on injury control. WHO's concern for injuries was reflected in this year's World Health Day (see the January–February 1993 issue of *World Health*).

A motorcyclist is much less likely to be killed, severely injured or disabled if wearing a helmet correctly. More and more people are cycling, not only for leisure, but also to get to their place of work, as in many developing countries. Severe brain injuries can result from accidents involving cyclists. In Australia, in the State of Victoria, legislation to make the wearing of bicycle helmets compulsory has led to fewer and less severe injuries. In any case, the wearing of helmets protects both your head and your life.

The WHO-sponsored Helmet Initiative has two major goals: to promote the use of bicycle and motorcycle helmets throughout the world, and to stimulate public health agencies into addressing injury control issues. The newsletter of the WHO Helmet Initiative, *Headlines*, gives regular news about the Initiative. For more information, please contact Dr Philip Graitcer, Centers for Disease Control, Atlanta, Georgia 30333, USA (Fax 1 404 488 4349). ■

The lesson of a poliomyelitis outbreak in the Netherlands

A recent outbreak of poliomyelitis in the Netherlands, with 68 cases, has led to a warning by WHO on the dangers of incomplete immunization. "As long as even small pockets of unvaccinated persons exist, even the richest countries will be at risk of sudden outbreaks of poliomyelitis", said Dr R. H. Henderson, Assistant Director-General of WHO.

In the current outbreak, which has already cost the Dutch health services US$ 10 million, the national disease surveillance programme has registered 68 cases among children and adults spanning seven provinces out of 12. At least two persons are known to have died from the disease.

The overwhelming majority of the Netherland's population is immunized against poliomyelitis as a matter of course. But there are pockets in different provinces containing unimmunized populations. They belong to various religious groups which do not accept immunization on principle. In the current outbreak persons belonging to five different fundamentalist denominations were involved.

The last poliomyelitis outbreak in the Netherlands took place some 15 years ago. Then, as now, these particular groups were implicated. In 1979, the virus was carried from the Netherlands to North America by members of these communities visiting their relatives in Canada and in the USA. According to US data, this is what caused the last outbreak in the country, which happened among the Amish community in the state of Pennsylvania. The 1992–93 Dutch outbreak has placed the US disease surveillance system on alert but there have been no cases of poliomyelitis transmission reported so far.

WHO and its Member States proclaimed in 1988 their intention to rid the world of this major crippling disease by the year 2000. So far, the overall results have been encouraging. In the Western Hemisphere, which launched its own eradication efforts in 1985, not a single case of poliomyelitis has been diagnosed for nearly two years. In all WHO's regions around the world, reference laboratory services are being put in place. Annual immunization coverage of children in their first year of life reached the 80% mark in 1990 and the number of cases reported has fallen dramatically.

But the recent outbreak in the Netherlands demonstrates the pitfalls on the road to eradication. "What is important", says Dr Robert Kim-Farley, Director of WHO's Expanded Programme on Immunization, "is to see the Dutch incident in the global perspective. Our Dutch colleagues managed not only to contain the outbreak but to deal with it in a very efficient and professional way. The lesson for the world, however, is that until the planet is totally free of poliomyelitis, even the best-immunized countries will be at risk of imported infections and epidemics".

Corrigendum

An error unfortunately appeared on page 19 of our September–October 1992 issue. Mr Badara Samb, noted in the text at the foot of the page as being Head Nurse at Ziguinchor Hospital in the Department of Oussouye, Senegal, is, in fact, in charge of the project "School of health development". ■

In the next issue

WHO's *Eighth report on the world health situation* covers the years 1985–90. The May–June issue of *World Health* will review some of the more outstanding achievements that took place during this five-year period. ■

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